**Toxicology Forum Nomination Form**

**Winter DC / Year**

**½ Day**

**Title of Session: ADVANCING RISK ASSESSMENT APPROACHES IN THE 21ST CENTURY**

**Why Session Important / Timely:** Recent findings from NAS committees (2007 and 2009) have prompted a renewed interest in refining risk assessment methods. In fact, other expert bodies have also delved into these areas and many consensus, and conflicting, positions have arisen. The Toxicology Forum would be an ideal venue for confirming consensuses and sounding out conflicting positions.

**Scientific / Mechanistic Interest:** Risk assessment methods need to be well founded in the underlying sciences of toxicology, epidemiology, exposure assessment, among others. Expert bodies are by definition limited to the experts on the panel and some risk assessment issues exceed the ability of any one panel to fully address. Thus, additional scientific discussion, debate, and resolution are needed.

**Regulatory Agency Impacted:** U.S. Environmental Protection Agency (EPA), other U.S. federal agencies and other world health agencies will be interested in this session.

**Summary of Session / Abstract:**

Informed risk-based regulatory decisions should be made in the most expert way since they are precipitated by real and perceived threats to human health, often under the glare of public scrutiny. Human risk characterization is based on a series of complex questions that risk assessors and mangers ask about soundness of scientific information related to hazard, dose-response and exposure assessment. Each question calls for a careful analysis and interpretation of available studies and selection of the data that are most scientifically reliable and pertinent to the problem in hand. The risk manager integrates information from preceding components of risk characterization, including uncertainty and variability, and synthesizes an overall conclusion about risk that is complete, informative, transparent and useful for risk-based management control options. Multiple organizations (Environmental Protection Agency, Alliance for Risk Assessment, Health and Environmental Sciences Institute, National Institute of Environmental Health Sciences/National Toxicology Program, NIH/Chemical Genomics Center, NIH/National Human Genome Research Institute and Food and Drug Administration) and stakeholders (academia, industry and NGOs) have been actively addressing recent recommendations

presented by the National Research Council relative to the use and utility of risk assessment in risk-based decision making through new and improved risk assessment approaches for both single chemicals and their mixtures. This timely workshop will bring together several of the organizations to discuss their efforts to promote the use and utility of emerging risk assessment approaches for informing risk management decisions in the 21st Century.

**Proposed Speakers:**

**Chairperson:**
**Chair Name:** Edward Ohanian, Ph.D.
**Chair Affiliation:** U.S. Environmental Protection Agency (EPA)
**Chair Email:** Ohanian.edward@epa.gov

**Cochair Name:** Michael Dourson, Ph.D.
**Cochair Affiliation:** Toxicology Excellence for Risk Assessment
**Cochair Email:** dourson@tera.org

**Speakers:**

**Name:** Julie Fitzpatrick, M.S. and Weihsueh Chiu, Ph.D.
**Affiliation:** U.S. Environmental Protection Agency (EPA)

**Phone:** 202-564-4212
**Fax:** 202-564-2070
**E-mail:** Fitzpatrick.julie@epa.gov

**Presentation Title:** EPA Framework for Human Health Risk Assessment to Inform Decision Making

**Presentation Description:** The Framework for Human Health Risk Assessment to Inform Decision Making being developed by the EPA Risk Assessment Forum incorporates recommendations presented in the National Research Council's 2009 report *Science and Decisions: Advancing Risk Assessment* on improving the utility of risk assessment and stakeholder involvement. Specifically to adopt a framework for risk-based decision-making that embeds the Red Book risk assessment paradigm that highlights the important roles of planning and scoping as well as problem formulation in designing risk assessments that will serve their intended purpose. The Framework for Human Health Risk Assessment to Inform Decision Making is intended both illustrate and foster increased implementation of existing EPA guidance for conducting risk assessments for human health and is expected to increase the transparency of the Human Health Risk Assessment and decision making processes at the Agency. The EPA Risk Assessment Forum also has developed a dose-response matrix that describes the current practices with respect to dose response assessment across EPA's programs and regions and to conduct "state-of-the-science" reviews that will explore new science that could

potentially impact dose response assessment. The "state-of-the-science" reviews are expected to focus on a particular endpoint/outcome and include the available science and interactions relative a range of factors (e.g., genetics, life-stage, background risk factors, nutrition, chemical agents, and non-chemical stressors)

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**Name:** Bette Meek, Ph.D.
**Affiliation:** McLaughlin Centre for Population Health Risk Assessment, University of Ottawa, Ottawa, ON, Canada

**Phone:** 613-562-5800
**Fax:** (none)
**E-mail:** bmeek@uottawa.ca

**Presentation Title:** Problem Formulation to Dose-Response: Advances via the *ARA* Beyond Science and Decisions Workshops

**Presentation Description:** Important recommendations of the 2009 NRC report, *Science and Decisions: Advancing Risk Assessment,* were to improve both the technical analysis that supports risk assessment and the utility of risk assessment. This presentation will discuss approaches to move the science of dose-response assessment forward, based in part on a three workshop series with over 45 sponsoring organizations conducted under the aegis of the Alliance for Risk Assessment (*ARA*). Twenty-four case studies were evaluated by a science panel, and the panel developed both a consensus on purpose-specific dose-response methods and a framework into which these case studies are fit. Several case studies will be used to highlight the framework including consideration of relevant data, the characterization of assumptions, strengths and limitations, and display of techniques that address key considerations in the dose-response.

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**Name:** John Doe, Ph.D.
**Affiliation:** Parker Doe Partnership LLP

**Phone:** +44 7860 907484
**Fax:** None
**E-mail:** john.doe@parkerdoe.com

**Presentation Title:** Development of an Integrated Evaluation Strategy for the 21st Century: Advances via the HESI RISK21 Project

**Presentation Description:** A novel integrated evaluation strategy framework will be presented in this session that represents the overarching product of the HESI Risk Assessment in the 21st Century (RISK21) effort. The framework is aimed at increasing

the degree of certainty that strategically derived data for human health risk assessment will be protective of public health. This concept is a shift away from traditional linear, tiered approaches that are reliant on apical toxicity endpoints from extensive animal testing, and towards a more probabilistic approach that assimilates exposure and dose-response information to determine the likelihood of adverse effects in likely exposure and use conditions. This dynamic framework draws upon existing knowledge gained over the past 30 years of toxicity and exposure assessment as a foundation, along with the incorporation of new 21st Century methodologies as they become available. In addition, the application of this framework to various risk assessment contexts, such as cumulative risk, will be explored.

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**Name:** Linda Birnbaum, Ph.D.
**Affiliation:** National Institute of Environmental Health Sciences

**Phone:** 919-541-3201
**Fax:** 919-541-2260
**E-mail:** birnbaumls@niehs.nih.gov

**Presentation Title:** Translating the Molecular Basis of Hazard to 21st Century Risk Assessment Approaches: Advances via Tox21 Project

**Presentation Description:** The goal of the NIEHS/NTP Tox21 Project is to move toxicology from a predominantly observational science at the level of disease-specific models to a predominantly predictive science focused upon a broad inclusion of target-specific, mechanism-based, biological observations. The ability to incorporate toxicity pathway-based in vitro data into risk assessment should make the assessment more robust while saving time and costs. However, the lack of xenobiotic metabolism in most in vitro assays and difficulties in extrapolating from in vitro concentration to in vivo dose must be overcome to make the in vitro data more useful. Another concern is the current requirement for demonstrating an adverse health outcome for many regulations, an endpoint not possible *in vitro*. Ultimately, we expect that the data generated by Tox21 will be useful in predicting the risks associated with environmental agents and their effects on especially sensitive populations.

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**Name:** Richard A. Becker, Ph.D., DABT (presenter); co-authors Robert Fensterheim, Ph.D., and Lynn H. Pottenger, Ph.D. DABT

**Affiliation:** American Chemistry Council (Becker)

**Phone:** 202-249-6405 (Becker)
**Fax:** None
**E-mail:** Rick_Becker@americanchemistry.com (Becker)

**Presentation Title:** Improving Risk Assessment Policies and Practices to Meet the Challenges Posed by 21st Century Science

Richard A. Becker, Ph.D. DABT, Robert Fensterheim, Ph.D., and Lynn H. Pottenger, Ph.D. DABT

**Presentation Description**: To harness the 21st century knowledge provided by advanced research methods for evaluating dosimetry and mechanisms of chemical interactions with, and potential effects upon, biological processes requires improvements in integrating the science into regulatory programs. There must be both a structural means and a willingness within programs to enable this. Mechanistic and computational screening assays provide qualitatively different information than in vivo apical tests, and the results from these dissimilar assays should be applied within a framework that is consistent with current scientific understanding of toxicological responses. Assuring the quality, objectivity, utility, transparency, and integrity of risk assessment practices, and incorporating all of these into decision-making, are objectives shared by all stakeholders. Through this lens, we will discuss opportunities for modernizing risk assessment science policies and practices, beginning with the initial problem formulation stage, and continuing through data acquisition and evaluation, peer review (and response to review), to final publication / dissemination of the risk assessment report.

**Funding: Identify Support for the Session:**

**1. U.S. Environmental Protection Agency (EPA)** is considering a grant or purchase order to fund this work.

**2. Toxicology Excellence for Risk Assessment (TERA)** will provide in kind support to co-ordinate this effort.